Remarks

Claims 123-143 are pending in this application. Upon reconsideration, the Examiner modified the species requirement to permit examination of polypeptides SEQ ID NOs: 1-7, and autoimmune disease such as those recited in claims 134-142. Claim 143 has been withdrawn from consideration as directed to non-elected subject matter. By this amendment, applicants have amended claims 126 and 128 without disclaimer or prejudice to applicants' rights to pursue the subject matter of these claims in this or another application. Applicants have also amended claims 123 and 133-134 and 142 and add new claims 144-166. Thus, claims 123-125, 127 and 129-166 are pending in this application.

Support for the amendment to claim 142 may be found, *inter alia*, on page 16, lines 15-16.

Support for new claims 144 and 158 may be found, *inter alia*, on page 17, lines 22-31.

Support for new claims 145-146 and 159-160 may be found, *inter alia*, on page 17, lines 22-23.

Support for new claims 147 and 161 may be found, *inter alia*, on page 17, lines 22-24.

Support for new claims 148, 150, 162 and 164 may be found, *inter alia*, on page 17, lines 22-26.

Support for new claims 149 and 163 may be found, *inter alia*, on page 17, lines 22-25.

Support for new claims 151 and 165 may be found, *inter alia*, on page 17, lines 22-27.

Support for new claim 152 may be found, *inter alia*, on page 13, lines 25-26, page 14, Table 1, page 16, lines 18-21, page 17, lines 18-21, and page 37, line 24 to page 38, line 27.

Support for new claim 153 may be found, *inter alia*, on page 41, lines 1-2.

Support for new claim 154 may be found, *inter alia*, on page 41, lines 4-5.

Support for new claim 155 may be found, *inter alia*, on page 13, lines 25-26 and page 14, lines 8-9.

Support for new claim 156 may be found, *inter alia*, on page 13, lines 25-26 and page 14, lines 14-15.

Support for new claim 157 may be found, *inter alia*, on page 13, lines 25-26, page 14, Table 1, page 16, lines 1-2 and 18-21, page 17, lines 18-21, and page 37, line 24 to page 38, line 27.

Support for new claim 166 may be found, *inter alia*, on page 18, lines 8-10 and 14-15 and page 16, lines 15-16.

Objection to Drawings

The Examiner rejected the drawings, filed 3/23/01, referring to PTO 948, Notice of Draftsperson's Patent Drawing Review. The Examiner required that the drawings be corrected.

In response, applicants attach hereto as **Exhibit 3** corrected

drawings.

Objection to Specification

The Examiner objected to the disclosure because of the following alleged informality: "This application is a continuation of PCT International Application No. PCT/US99/22402... incorporated by reference into the present application" filed by preliminary amendment A on page 1 after the title should be deleted because it is redundant in the subsequent paragraph that discloses "The present application claims the benefit of US Provisional Application... incorporated by reference into the present application" under the heading Related Application as amended by amendment B filed 8/6/02. The Examiner required that appropriate action be taken.

In reply, applicants have amended the specification as suggested by the Examiner. Therefore, applicants respectfully request that the objection be withdrawn.

Information Disclosure Statements

The Examiner stated that the references on the Form-PTO 1449, filed 8/26/02, 9/16/02, and 10/23/02, have been crossed out because none of the references have been submitted to the Office.

In response, applicants attach hereto postcard receipts for the above-listed Information Disclosure Statements showing receipt by the U.S. Patent and Trademark Office of the Information Disclosure Statements and references. Applicants submit herewith courtesy copies of the Information Disclosure Statements and references.

Claim Objection

The Examiner objected to claim 134 is because "rheumatoid arthritis" is recited twice.

In reply, applicants have amended claim 134 by removing the second recitation of "rheumatoid arthritis." Accordingly, applicants respectfully request that the Examiner withdraw this objection.

Enablement Rejections under 35 U.S.C. § 112, First Paragraph

Overview

The Examiner rejected claims 123-142 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for a method for treating an autoimmune disease wherein the autoimmune disease is acute multiple sclerosis in a mammal comprising administering to the mammal a purified polypeptide comprising the amino acid sequence of SEQ ID NOs: 2 and 7, does not reasonably provide enablement for (1) a method of treating or preventing any autoimmune disease in any mammal comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NOs: 1-7 or a mixture of purified polypeptides; (2) said method wherein the purified polypeptide consists entirely of L-amino acids or D-amino acids; (3) a method of treating or preventing any autoimmune disease in any mammal comprising administering to the mammal a pharmaceutical composition consisting essentially of any purified polypeptide having the amino acid sequence set forth in SEQ ID NOs: 1-7 or a mixture of purified polypeptides, and a pharmaceutically acceptable carrier; (4) a method of preventing any autoimmune disease such as any B cell

mediated autoimmune disease, any T cell mediated autoimmune disease, any demyelinating disease, any inflammatory disease, any autoimmune disease such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NOs: 1-7, and (5) a method of "treating" any autoimmune disease such as any B cell mediated autoimmune disease, any T cell mediated autoimmune disease, any demyelinating disease, any inflammatory disease, rheumatoid arthritis, osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NOs: 1-7. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner noted that factors to be considered in determining whether undue experimentation is required to practice the

claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The Examiner alleged that the factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The Examiner alleged that the specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Treatment and Prevention of EAE

The Examiner alleged that the specification discloses only a method for treating female (SJL/J x BALB/c) mice with mouse spinal cord homogenate to induce EAE, which is a model for acute multiple sclerosis, and a polypeptide selected from the group consisting of SEQ ID NOs: 2, 4, 5, 6 and 7. The Examiner alleged that the results in Table 14 on page 38 show that only polypeptides of SEQ ID NOs: 2 and 7 block the progression of EAE while treatment with polypeptides of SEQ ID NOs: 4, 5 and 6 fail to block the progression of EAE. The Examiner alleged that treatment with polypeptides of SEQ ID NOs: 4-6 does not prevent EAE because the mean onset of EAE occurred on days 11.7, 14, and 12, respectively, as compared to the control (11.3 days). The Examiner alleged that the delayed onset of disease for polypeptides of SEQ ID NO: 4 and 6 is not significantly different than the control. The Examiner alleged that the block in the progression of disease in the treatment using polypeptides of SEQ ID NO: 2 and 7 could be simply due to a delay in the onset of EAE because there allegedly is insufficient information on the time course in the specification as filed and about relapse.

The Examiner alleged that, even if the method is limited to treating multiple sclerosis, the specification on page 38 discloses that only two (SEQ ID NO: 2 and 7) out of seven polypeptides could block EAE. However, the method of treating EAE with polypeptides of SEQ ID NO: 4, 5 or 6 delays the onset of disease with varying degree of blocking while polypeptides of SEQ ID NO: 1 and 3 have no *in vivo* data.

In response, applicants point out that the specification demonstrates that polypeptides of SEQ ID NOs: 2, 4-6 and 7 treat EAE. Applicants point out that Table 14 of the subject specification shows a significant effect on the mean EAE disease score for the tested polypeptides of the subject invention in comparison to the control. Table 14 shows that the mean score for the control was 4.9 on a 0-5 scale of disease severity, with 5 being the most severe, i.e., death. However, the mean scores for polypeptides of SEQ ID NOs: 2, 4, 5, 6, and 7 were 0, 2.8, 0.2, 0.7, and 0, respectively. Thus, the subject specification shows that polypeptides of SEQ ID NOs: 2, 4, 5, 6, and 7 are all effective in the treatment of EAE because the mean disease severity score is significantly lower in the mice treated with the polypeptides as compared to the control. Therefore, applicants contend that amended claims 123 and 133, directed to a method of treating an autoimmune disease with polypeptides of SEQ ID NOs: 2, 4-6 and 7 are enabled.

Applicants further point out that the specification shows that polypeptides of SEQ ID NOs: 2, 4-6 and 7 delay the onset of EAE. Table 14 demonstrates that polypeptides of SEQ ID NOs: 2 and 7 are effective in delaying the onset of EAE because the mice that received these polypeptides did not exhibit any clinical signs of EAE during the course of the experiment, while the control

mice had a mean disease onset of 11.3 days. Additionally, Table 14 demonstrates that polypeptides of SEQ ID NOs: 4-6 delayed the onset of EAE from that of the controls (11.3 days) to 11.6, 14.0 and 12.0 days, respectively. To counter the Examiner's allegation that the delay in onset of EAE for polypeptides of SEQ ID NOs: 4 and 6 does not differ significantly from that of the controls, applicants respectfully direct the Examiner's attention to Table 14, which demonstrates that 4 out of 10 mice treated with SEQ ID NO: 4 did not develop clinical symptoms of EAE and 7 out of 10 mice given SEQ ID NO: 6 did not show clinical symptoms of EAE, while every control mouse exhibited clinical symptoms of EAE. Thus, in the mice that received peptides of SEQ ID NOs: 4 and 6 and did not show clinical symptoms of EAE, the onset of EAE was, at minimum, delayed beyond the conclusion of the experiment. This delay in onset of EAE is, in fact, significantly better than the controls, all of which presented EAE symptoms. Accordingly, applicants contend that claims 152 and 157, directed to a method of delaying the onset of an autoimmune disease with polypeptides of SEQ ID NOs: 2, 4-6 and 7 are enabled.

Prevention of Autoimmune Disease

The Examiner alleged that the specification does not teach a method of preventing any autoimmune disease mentioned above because of the following reasons: The Examiner alleged that there is insufficient guidance and *in vivo* working examples that the claimed method of using any polypeptides mentioned above could "prevent" any autoimmune disease. The Examiner alleged that the term preventing as defined in the Webster's II New Riverside University Dictionary on page 933 as "to thwarting or warding off illness or disease". The Examiner alleged that the specification discloses in Table 14 on page 38 that treatment

with polypeptides of SEQ ID NO: 4-6 does not "prevent" EAE, but rather the treatment delays the onset of EAE by 1 to 3 days where the EAE model is a model for early onset of multiple sclerosis.

In reply, applicants note that the new claims of the subject application are directed to a method of delaying the onset of an autoimmune disease by administering polypeptides of SEQ ID NOs: 2, 4-6 and 7. As discussed above and as acknowledged by the Examiner, delaying the onset of autoimmune disease with these polypeptides is enabled.

EAE as Model for Autoimmune Diseases, Including Multiple Sclerosis

The Examiner alleged that the EAE model used by applicants is not appropriate for chronic relapse autoimmune disease, or any other disease such as the ones recited in claim 134. Further, the Examiner alleged that the experiments were not carried out long enough to see the effect of polypeptide of SEQ ID NO: 2 and 7 on chronic relapsing multiple sclerosis. The Examiner alleged that, in humans, the claimed autoimmune diseases encompassed by the claimed method are already established before therapy is offered. The Examiner alleged that it is not clear that administering the claimed polypeptides shortly after (48 hours) or simultaneously with mouse spinal cord homogenate to induce acute onset of EAE accurately reflects the chronic relapsing nature of autoimmune disease.

The Examiner also alleged that Van Noort et al. teach that the type of EAE induced is dependent on the immunization protocol, animal strain, and antigen used and that some antigens, such as MBP, resulted in an acute episode of EAE, while others induced a

chronic relapsing disease, citing page 169, first full paragraph, in particular. The Examiner alleged that Van Noort et al. further teach that it is the chronic relapsing EAE that is reminiscent of multiple sclerosis (MS) because animals develop accumulating neurological features of the induced disease, citing page 169, first full paragraph, in particular.

The Examiner also alleged that Pender et al. teach that many therapies that are effective in the animal model such as EAE, are either ineffective in multiple sclerosis or in the case of gamma interferon, lenercept and altered peptide ligands, actually make multiple sclerosis worse, citing the abstract, in particular.

- EAE is a Model for Demyelinating Diseases, Including Multiple Sclerosis

In reply, applicants respectfully direct the Examiner's attention to MPEP § 2164.02, which states:

> [...] if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the examiner has evidence that it does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

Applicants point out that EAE is generally recognized in the art as correlating to demyelinating diseases, including multiple sclerosis, as evidenced by Lisak et al. (Exhibit 55 of August 1, 2002 Information Disclosure Statement, a courtesy

copy of which is being submitted herewith) and Sela et al. (Exhibit 82 of August 1, 2002 Information Disclosure Statement). Additionally, Van Noort et al. describe EAE as an accepted model for multiple sclerosis (page 167-174). Additionally, on page 129, last paragraph to page 130, first paragraph, Van Noort et al. state that in multiple sclerosis, "experimental models, both viral and autoimmune, have defined the importance of both autoreactive T cells and autoantibodies and other contributing factors," thus showing their affirmance of the reliability of experimental models for multiple sclerosis, including EAE. This reliance is echoed on page 197, second paragraph, which states that in multiple sclerosis, that "the activation of specific populations of helper T lymphocytes must be instrumental in disease development...can now be safely concluded based on detailed immunohistochemical studies on inflammatory disease lesions, the clear association of autoimmune diseases with genes that encode HLA-DR molecules, and experiences with animal models that provide us with the best clinical and pathological similarities to human diseases" [emphasis added]. Therefore, applicants contend that the EAE is accepted in the scientific community as a model for multiple sclerosis.

Contrary to the Examiner's allegation based on Van Noort et al. that MBP-induced EAE is not an appropriate model for "chronic relapsing" multiple sclerosis, applicants contend that MBP-induced EAE is an appropriate model for multiple sclerosis, including the type referred to by Van Noort et al. as "chronic relapsing." Applicants first note that "chronic relapsing EAE," as used by Van Noort et al., actually refers to relapsing-remitting EAE. Van Noort et al. explain this connotation on page 169, paragraph 2, where the course of chronic relapsing EAE is described as acute, followed by

resolution of disease state, followed by relapses. As evidence that MBP-induced EAE is an appropriate model for relapsing-remitting multiple sclerosis, applicants attach hereto as **Exhibit 4** a copy of Fritz et al., which reports that MBP can induce relapsing-remitting EAE. For instance, Fritz et al. noted that mice had frequent relapses after remission from MBP-induced EAE. Fritz et al. also reported that rats showed signs of relapse after remission from MBP-induced EAE. Additionally, Fritz et al. noted that recurrent EAE was induced in rats after MBP administration.

In further contradiction to the Examiner's allegation that MBP-induced EAE is not an appropriate model for relapsing-remitting multiple sclerosis and Van Noort et al.'s suggestion on page 172 that MBP-induced demyelination produces very little, if any, demyelination, which the reference asserts to be "the hallmark of MS" (page 172), applicants attach hereto as **Exhibit 5** a copy of Pender, which asserts that MBP-induced EAE results in ample demyelination in the central and peripheral nervous systems of rats. Pender postulates that the reported absence of demyelination in MBP-induced EAE may, in fact, be the failure to detect demyelination due to inadequate and incomplete histological examination.

- Autoimmune Diseases Other than Multiple Sclerosis

The Examiner alleged that Van Noort et al. teach that EAE is only a model for acute multiple sclerosis and the model is not appropriate for other autoimmune diseases such as rheumatoid arthritis, osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes

mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity, citing page 167, bridging page 168, Table III, in particular. Further, the Examiner alleged that there is no guidance and working example demonstrating that any of the polypeptides such as SEQ ID NO: 1-7 could treat or prevent any disease mentioned above.

The Examiner additionally alleged that, even if the method is limited to a method of treating autoimmune disease by administering a polypeptide selected from the group consisting of SEQ ID NO: 2 and 7, it is not clear that reliance on the EAE experimental model, which is a model for acute multiple sclerosis, accurately reflects other autoimmune disease such as the ones recited in claims 134-142 since the EAE model is allegedly irrelevant to other diseases such as the ones recited in claim 134-142 and the prevention of chronic relapse multiple sclerosis.

The Examiner alleged that, given the infinite number of autoimmune diseases, the limited working example and the unpredictable nature of the polypeptide even for just multiple sclerosis, a person of skill in the art could not predict which particular amino acid sequences of the claimed polypeptides are effective for treating EAE, let alone treating or preventing any autoimmune disease as encompassed by the claimed method.

For these reasons, the Examiner alleged that it would require undue experimentation for one skilled in the art to practice the claimed invention, citing page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The Examiner alleged that the more unpredictable the area is, the more specific enablement is necessary, citing *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The Examiner asserted that, in view of the alleged quantity of experimentation necessary, the alleged limited working example, the alleged unpredictability of the art, the alleged lack of sufficient guidance in the specification and the breadth of the claims, it allegedly would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

In response, applicants point out that Tisch and McDevitt, copy previously submitted, refer to EAE as a "model of autoimmunity" on page 438, column 1, paragraph 2, as applicants discussed in the August 1, 2002 Response to the July 1, 2002 Office Action. Additionally, Aharoni et al. states that suppressor cell activity has been shown in the EAE model in mice and rats and has been suggested in other autoimmune diseases. Aharoni et al. also report that the relapses and remissions often occur in multiple sclerosis and in other autoimmune diseases. The reference also states that these relapses and remissions have been explained by changes in the suppressor cell population. Thus, EAE and autoimmune diseases involve the same mechanism. This yet further support applicants contention that EAE is an appropriate model for autoimmune diseases. A copy of Aharoni et al. may be found in Exhibit 110 of August 1, 2002 Information Disclosure Statement, a courtesy copy of which is being submitted herewith.

Furthermore, Copolymer 1 has been suggested for the treatment of autoimmune diseases (Kipnis and Schwartz), and the polypeptides of the subject invention correspond to Copolymer 1 as explained below. For example, Kipnis and Schwartz

suggested that Copolymer 1 acts as a "universal antigen" by weakly activating a wide spectrum of self-reactive T cells. A copy of Kipnis and Schwartz is attached hereto as **Exhibit 6**.

Regarding the correspondence between Copolymer 1 and the polypeptides of the subject invention, applicants note that the polypeptides correspond to Copolymer 1 in amino acid composition and molar fraction, as disclosed in the subject specification on page 3, lines 13-19, page 4, line 24-28, page 5, lines 18-24, page 13, lines 25-26 and page 14, Table 1. Thus, Copolymer 1 and the polypeptides of the subject invention consist of glutamic acid, lysine, alanine and tyrosine (see page 3, lines 13-19 and page 14, Table 1). The molar fractions in Copolymer 1 are 0.427 alanine, 0.141 glutamic acid, 0.093 tyrosine and 0.337 lysine, while the molar fractions of the polypeptides of the subject invention are 0.38 to 0.50 alanine, 0.13 to 0.15 glutamic acid, 0.08 to .10 tyrosine and 0.3 to 0.4 lysine (see page 3, lines 13-19, page 5, lines 18-24 and page 13, lines 25-26). The molecular weight of copolymer 1 is 4,000 to 13,000 daltons (see page 3, lines 13-17), and the polypeptides of the subject invention have a molecular weight of 2,000 to 40,000 daltons (see page 4, lines 24-28).

Further evidence of the correspondence between the polypeptides of the subject invention and Copolymer 1 may be found on page 35, line 11 to page 36, line 18 of the subject specification, which shows that the polypeptides of the subject invention were recognized by monoclonal antibodies against Copolymer 1. Furthermore, two out of four T cell lines specific to Copolymer 1 recognized the polypeptides of the subject invention, as demonstrated on page 36, line 20 to page 37, line 22 of the subject specification.

PCT International Publication No. WO 00/05250, a copy of which is attached hereto as **Exhibit 7**, teaches that Copolymer 1 is useful in the treatment and prevention of autoimmune diseases and specifically lists all of the autoimmune diseases enumerated in claim 134 of the subject application. The publication states:

> The pathological process of autoimmune diseases and immune rejection is mediated by T cells. Upon binding to and recognition of an antigen, T cells proliferate, secrete cytokines and recruit additional inflammatory and cytotoxic cells to the site...[Copolymer 1] prevent[s] T cell proliferation and T cell functions such as cytokine secretion and recruitment of inflammatory and cytotoxic cells to the site (page 20, lines 17-20).

PCT International Publication No. WO 00/05250 demonstrates the inhibition of T cell proliferation and cytokine secretion in its examples. Example 6 of the publication shows that Copolymer 1 inhibits the proliferation of T cells specific to MBP, which has been suggested as an autoantigen in multiple sclerosis. Example 9 of the publication demonstrates that Copolymer 1 inhibits the IL-2 production of collagen-specific T cells in response to collagen, which is implicated in the autoimmune disease, rheumatoid arthritis. Example 10 of the publication shows that Copolymer 1 also inhibits the production of IL-2 by T cells specific to the myasthenia gravis peptide, p259. Myasthenia gravis is an autoimmune disease.

As the Examiner is aware, the enablement of a representative

number of species within a genus enables the genus (MPEP § 2164.02). Accordingly, applicants respectfully submit that the enablement requirement is satisfied for the claims as amended.

Immune Response

Delayed-type-hypersensitivity (DTH) responses operate on the same principles as autoimmune responses (proliferation and secretion of cytokines by T cells in response to an antigen) (C. Allen Black). Hence, applicants assert that the treatment and prevention of DTH with the polypeptides of the subject invention is also enabled. A copy of C. Allen Black is attached hereto as **Exhibit 8**.

Applicants respectfully submit that the subject application also enables the treatment and prevention of host-versus-graft-disease (HVGD) and graft-versus-host-disease (GVHD). Schlegel et al. disclose that GLAT, or Copolymer 1, is effective in the prevention of GVHD. The polypeptides of the subject invention correspond to Copolymer 1 as described above. A copy of Schlegel et al. may be found in Exhibit 132 of the August 1, 2002 Information Disclosure Statement, a courtesy copy of which is being submitted herewith. In addition, Aharoni et al. teach that a copolymer comprised of the four amino acids in Copolymer 1 in similar molar ratios treats GVHD. A copy of Aharoni et al. may be found in Exhibit 144 of the August 1, 2002 Information Disclosure Statement, a courtesy copy of which is being submitted herewith. PCT International Publication No. WO 00/27417 discloses that Copolymer 1 treats and prevents GVHD and HVGD. A copy of PCT International Publication No. WO 00/27417 may be found in Exhibit 24 of the August 1, 2002 Information Disclosure Statement, a courtesy copy of which is being submitted

herewith.

For all of the above reasons, applicants respectfully request that the Examiner withdraw the enablement rejections.

Written Description Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 123-142 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner alleged that the specification does not reasonably provide a written description of: (1) a method of treating or preventing any autoimmune disease in any mammal comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7 or a mixture of the purified polypeptides; (2) said method wherein the purified polypeptide consists entirely of L-amino acids or D-amino acids; (3) a method of treating or preventing any "autoimmune disease" in any mammal comprising administering to the mammal a pharmaceutical composition consisting essentially of any purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7 or a mixture of the purified polypeptides, and a pharmaceutically acceptable carrier; (4) a method of preventing any autoimmune disease such as any B cell mediated autoimmune disease, any T cell mediated autoimmune disease, any demyelinating disease, any inflammatory disease, any autoimmune disease such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune hemolytic anemia, autoimmune oophoritis,

autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7, and (5) a method of "treating" any autoimmune disease such as any B cell mediated autoimmune disease, any T cell mediated autoimmune disease, any demyelinating disease, any inflammatory disease, rheumatoid arthritis, osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7.

The Examiner alleged that the specification discloses only a method for treating female (SJL/J x BALB/c) mice with mouse spinal cord homogenate to induce EAE, which is a model for multiple sclerosis, and a polypeptide selected from the group consisting of SEQ ID NO: 2, 4, 5, 6 and 7. The Examiner alleged that the results in Table 14 show that only polypeptides SEQ ID NO: 2, and 7 block the progression of EAE while treatment with polypeptides of SEQ ID NO: 4, 5 and 6 fail to block the progression of EAE, referring to page 38. The Examiner alleged that treatment with polypeptides of SEQ ID NO: 4-6 does not prevent EAE because it has a mean onset of EAE at days 11.7, 14,

and 12, respectively, as compared to control (11.3 days). The Examiner alleged that the delayed onset of disease for polypeptides of SEQ ID NO: 4 and 6 is not significantly different than the control. The Examiner alleged that the block in the progression of disease is the treatment using polypeptides of SEQ ID NO: 2 and 7 could be simply due to a delay in the onset of EAE because there allegedly is insufficient information on the time course in the specification as filed, much less about relapse.

The Examiner alleged that, with the exception of the specific method of treating multiple sclerosis by administering the specific polypeptides mentioned above, there allegedly is insufficient written description about the method of treating any autoimmune disease such as any B cell mediated autoimmune disease, any T cell mediated autoimmune disease, any demyelinating disease, any inflammatory disease, rheumatoid arthritis, osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus, graft versus host disease (GVHD), host versus graft disease (HVGD) or delayed-type hypersensitivity comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7. Further, the Examiner alleged that there is insufficient written description about the method of preventing any autoimmune disease such as the ones recited in claims 134-142 comprising administering to the mammal a purified polypeptide having the amino acid sequence set forth in SEQ ID NO: 1-7. Further, the Examiner alleged that there is inadequate written description about the method of treating any autoimmune

disease mentioned above comprising administering any polypeptides such as SEQ ID NO: 1 and 3.

The Examiner alleged that the specification discloses only treating multiple sclerosis by administering polypeptides selected from the group consisting of SEQ ID NO: 2, 4, 5, 6 and 7 using the EAE as a model for multiple sclerosis. The Examiner alleged that, given the alleged lack of a written description of any additional representative species of autoimmune disease that can be treated or prevented using any polypeptide of SEQ ID NO: 1-7, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, the Examiner alleged that applicants were not in possession of the claimed genus, citing *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398.

In response, applicants respectfully direct the Examiner's attention to the Experimental Example on page 37, line 24 to page 38, line 27 of the subject application. As discussed above, the disease severity score in Table 14 on page 38 shows that polypeptides of SEQ ID NOs: 2 and 4-7 treated EAE, which, as previously described, is a model of demyelinating disease. Thus, applicants were in possession of the subject matter of amended claims 123 and 133 when the application was filed. As also mentioned previously, the disease severity score for polypeptides of SEQ ID NOs: 2 and 7 demonstrates that they prevented EAE. Therefore, applicants were in possession of the subject matter of new claims 146 and 151 at the time of filing the application.